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Featured Article

Alzheimer's disease assessment scale-cognitive 11-item progression model in mild-to-moderate Alzheimer's disease trials of bapineuzumab

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Abstract

Introduction: The objective of this study was to estimate longitudinal changes in disease progression (measured by Alzheimer's disease assessment scale-cognitive 11-item [ADAS-cog/11] scale) after bapineuzumab treatment and to identify covariates (demographics or baseline characteristics) contributing to the variability in disease progression rate and baseline disease status.

Methods: A population-based disease progression model was developed using pooled placebo and bapineuzumab data from two phase-3 studies in *APOE* ε4 noncarrier and carrier Alzheimer's disease (AD) patients.

Results: A beta regression model with the Richard's function as the structural component best described ADAS-cog/11 disease progression for mild-to-moderate AD population. This analysis confirmed no effect of bapineuzumab exposure on ADAS-cog/11 progression rate, consistent with the lack of clinical efficacy observed in the statistical analysis of ADAS-cog/11 data in both studies. Assessment of covariates affecting baseline severity revealed that men had a 6% lower baseline ADAS-cog/11 score than women; patients who took two AD concomitant medications had a 19% higher (worse) baseline score; *APOE* ε4 noncarriers had a 5% lower baseline score; and patients who had AD for a longer duration had a higher baseline score. Furthermore, shorter AD duration, younger age, *APOE* ε4 carrier status, and use of two AD concomitant medications were associated with faster disease progression rates. Patients who had an ADAS-cog/11 score progression rate that was not statistically significantly different from 0 typically took no AD concomitant medications.

Discussion: The beta regression model is a sensible modeling approach to characterize cognitive decline in AD patients. The influence of bapineuzumab exposure on disease progression measured by ADAS-cog/11 was not significant.

Trial Registration: ClinicalTrials.gov identifier: NCT00575055 and NCT00574132.

Keywords: ADAS-cog/11; Bapineuzumab; Alzheimer's disease; Disease progression model

1. Introduction

Disease-modifying therapies that can potentially alter the underlying progressive cytopathology and pathophysiology of Alzheimer's disease (AD) are being evaluated to slow or possibly arrest cognitive and functional decline. Because AD progresses very slowly, long-term data collection is required for accurately analyzing effects of novel modalities aiming to modify the underlying pathologic changes.

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One of the aims of this analysis was to understand patient heterogeneity in disease progression. This methodology is analogous to the exercise performed as part of the AD assessment scale-cognitive 11-item (ADAS-cog/11) quantitative clinical trial simulation model that was recently qualified by the Food and Drug Administration and European Medical Association, for mild-to-moderate AD [1–3]. So far, numerous model-based approaches have been proposed based on Alzheimer's Disease Neuroimaging Initiative data to investigate cognitive decline in AD patients [4–7]. Most of these models describe disease progression based on the longitudinal response in ADAS-cog/11 subscale. According to past reports, an overall annual worsening in the placebo group is estimated to be 5.5 points in ADAS-cog/11 score [8–10]. However, despite significant advancements in quantitative understanding of AD progression, it is important to understand how important covariates influence clinical outcomes of disease-modifying treatments. Many risk factors such as age, *APOE* ε4 genotype, gender, family history of AD, years of education, total serum cholesterol, executive function tests, instrumental activities of daily living [5,11], and baseline severity are thought to influence AD progression. Several of these covariates such as serum cholesterol, executive function tests, and activities of daily living could not be tested in the current analysis because they were not measured in studies 301/302. We, therefore, aimed to assess how important covariates influence disease progression parameters.

In the current analysis, we established a population-based pharmacodynamic disease progression model using pooled data from two phase-3 studies of bapineuzumab [12]. The objectives of this analysis were (1) To model disease progression in patients with mild-to-moderate AD, considering baseline disease status and change in cognition as a function of time; (2) To quantify different sources of variability such as demographics, number of copies of *APOE* ε4 allele, and other covariates that affect disease progression parameters; (3) To evaluate the magnitude and time course of the placebo response; (4) To assess missing data mechanisms; and (5) To estimate the impact of bapineuzumab on disease progression rate and assess whether its effect was influenced by baseline disease status.

2. Methods

2.1. Data sources

Pooled data from two phase-3 clinical studies of bapineuzumab were included in this analysis. These were 78-week, randomized, double-blind, placebo-controlled, parallel group studies that were conducted to investigate the efficacy and safety of bapineuzumab (0.5 or 1.0 mg/kg infused intravenously for 1 hour/13 weeks for six infusions) versus placebo in apolipoprotein E, ε4 allele (*APOE* ε4) noncarrier (study 301) or carrier (study 302) patients with mild-to-moderate AD. Mild versus moderate AD definitions were based on baseline mini-mental state examination (MMSE) score (mild AD: baseline MMSE $\geq$21 vs. moderate AD: baseline MMSE $<$21). The detailed inclusion and exclusion criteria and demographic and clinical characteristics used to build the statistical models and study designs for both studies are described in the primary publication [12].

ADAS-cog/11 [13] was used as a coprimary efficacy end point in both studies to measure cognitive performance in affected domains of AD from baseline to week 78. The database for this disease progression analysis comprised all ADAS-cog/11 measurements (weeks 0, 13, 26, 39, 52, 65, and 78) from studies 301 and 302 with an available date and time of testing.

2.2. Model building process

Model building was performed using a population pharmacokinetic/pharmacodynamic (PK/PD) approach (nonlinear mixed-effect modeling [NONMEM] version 7.1 with GFORTRAN compiler). Postprocessing of NONMEM output i.e. data set exploration, visualization, and diagnostic plot preparation were completed using S-Plus Professional version 6.2 (Insightful Corporation, Seattle, WA, USA), R version 2.13.2 (http://www.r-project.org), and Xpose package 4 (http://xpose.sourceforge.net). Briefly, a structural disease progression model was built using available blinded data set (301 and 302 studies), followed by incorporation of covariate components into the model, and modeling missing data effect using a hazard function with covariates affecting the hazard rate (Fig. 1). Model performance was evaluated by checking model diagnostics, assessing plausibility of the model parameters, and by performing visual predictive checks (VPC). After database lock and unblinding of both studies, the model was run on an entire database to obtain final parameter estimates and asymptotic standard errors, including the effect of bapineuzumab exposure on disease progression.

2.3. Population PK/PD model

2.3.1. Structural model selection

Eight possible structural models from previously published articles [5,7,14–16] were tested (Table 1) to select a single base model using the following criteria: (1) Akaike information criterion (AIC); (2) Goodness-of-fit diagnostics (η shrinkage); and (3) Ill conditioning and overparameterization by inspecting the eigenvalues of the covariance matrix (ratio of the largest eigenvalue to the smallest eigenvalue to be $<$1000).

2.3.2. Beta regression

As ADAS-cog/11 score is a bounded outcome, disease progression was expected to be nonlinear given the ceiling and floor effects [17]. Rogers et al. [18] proposed the use of beta-distributed residuals to model the heteroscedasticity

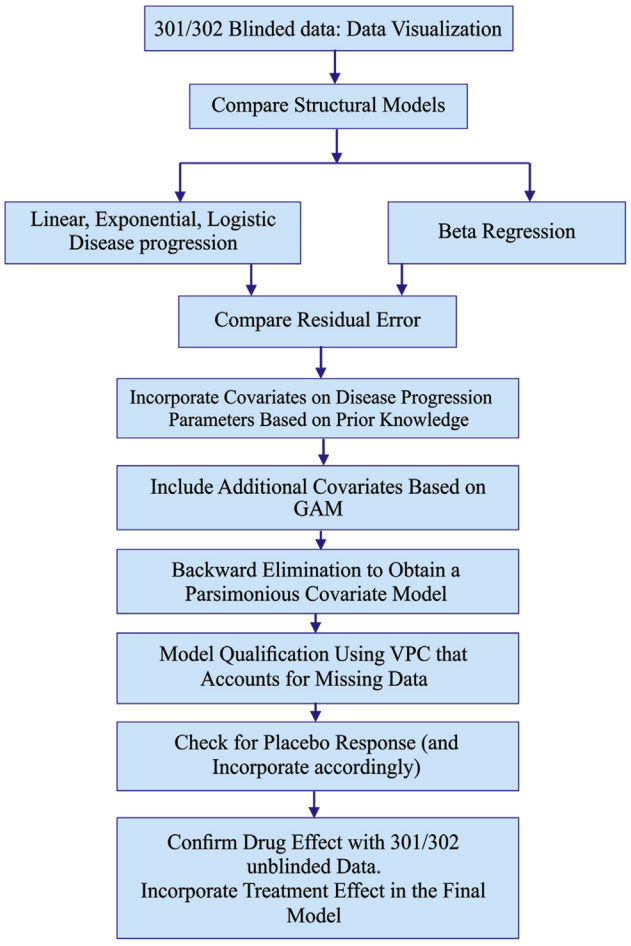

Fig. 1. Overview of model building process. Abbreviations: GAM, generalized additive modeling; VPC, visual predictive check.

in residual error and to limit ADAS-cog/11 predictions within the range of the original instrument. Beta regression models that could produce individual predictions within the boundaries were tested, and three such previously developed models [19] were compared against each other using AIC, η shrinkage, and condition numbers: (1) Richard's function [5,16]; (2) linear progression on a logit scale; and (3) linear progression on a logit scale with disease severity as a covariate on progression rate.

2.3.3. Residual error structure optimization

In this analysis, ADAS-cog/11 scores were normalized by dividing by 70 to ensure that the measurement unit for observations was the same across all models and to keep the dependent variable within a required range of 0–1 as per beta regression. Since log-normal, logit-normal, and beta residuals cannot handle data at the lower and/or upper boundaries, the boundary data were not incorporated into the residual error analysis initially for fair comparisons. The complete log-likelihood function ($L=\sum_i^n l_i$) for each distribution is listed in Table 2, the model with lowest L value was chosen for further development.

2.3.4. Handling boundary data

Some residual error models assumed that the dependent PD variable (ADAS-cog/11 score) was continuous in nature and that the data resided within boundaries of the scale. If log-normal, logit-normal, or beta residuals were found to have more suitable distribution, all data were rescaled by a small noise [$\delta = 0.01$] to use observations at boundaries of the scale (0.5% of the observations) in subsequent analysis. The δ moved the boundary of observations slightly within the edges and all rescaled data lay between 0 and 70, which was ADAS-cog/11 score range. This modification was performed using the scaling method [20], which suggested 0.01 is a reasonable choice for δ.

2.4. Modeling covariate effects

The covariates tested in this analysis were age, sex, *APOE* ε4 carrier status, years since AD onset (YSO), and AD concomitant medication use (cholinesterase inhibitors or memantine). Based on prior knowledge [4,5], the effects of four covariates (*APOE* ε4 carrier status [ε4 noncarrier, ε4 heterozygous, and ε4 homozygous], age, sex on progression rate, and YSO on baseline score) were embedded in the disease progression model to characterize their potential effects. Covariate screening was performed using generalized additive modeling ([GAM], implemented in the Xpose software), and GAM-selected covariates were included in the model via a full model/backward elimination approach [21]. A covariate was included only if the objective function value (OFV) increased by 7.88 points on its removal ($P < .005$ criterion) to avoid inclusion of insignificant effects into the model due to multiple comparisons integral to the backward elimination procedure. Continuous covariates were included in the model using the following equation:

$$\mathrm{TVP}=\theta_x \cdot \left(\frac{\text{Covariate}}{\text{Covariate median}}\right)^{\theta_y} \quad (1)$$

where, TVP: typical value of the parameter; thetas (θ): fixed-effect parameters.

The impact of baseline disease severity on progression rate was assessed either as a covariate (linear and beta regression models) or through the structural model (logistic and exponential models). Model selection was based on mechanistic plausibility, OFV, and AIC.

2.5. Missing data analysis

Because the analysis involved likelihood-based mixed-effects modeling, we assumed a missing at random (MAR) mechanism to capture missing data (e.g. dropout). This approach was consistent with primary statistical analysis of both studies in which a mixed-effect model with repeated measure (MMRM) model was proposed. The missing data analysis was primarily conducted to assess the missing

Table 1
Summary of structural models

Model description	Base models	Objective function value	Number of θs	AIC* value
Linear progression model #1 with shape parameter θ (Ito 2010)	$R_i(t) = R_{0i} + \alpha_i \cdot t + \varepsilon$ $R_{0i} = R_0 \cdot \exp(\eta_{1i})$ $\alpha_i = \alpha\left(\frac{bMMSE_i}{21}\frac{30-bMMSE_i}{9}\right)^{\theta} + \eta_{2i}$ $\eta_{1i} \sim N(0, \omega_1^2); \eta_{2i} \sim N(0, \omega_2^2); \varepsilon \sim N(0, \sigma^2)$	63,100.7	3	63,107
Linear progression model #2 with shape parameter θ1 (Ito 2010)	$R_i(t) = R_{0i} + \alpha_i \cdot t + \varepsilon$ $R_{0i} = R_0 \cdot \exp(\eta_{1i})$ $\alpha_i = \alpha\left(\frac{bMMSE_i}{21}\right)^{\theta 1}\left(\frac{30-bMMSE_i}{9}\right) + \eta_{2i}$ $\eta_{1i} \sim N(0, \omega_1^2); \eta_{2i} \sim N(0, \omega_2^2); \varepsilon \sim N(0, \sigma^2)$	63,126.2	3	63,132
Linear progression model #3 with shape parameter θ2 (Ito 2010)	$R_i(t) = R_{0i} + \alpha_i \cdot t + \varepsilon$ $R_{0i} = R_0 \cdot \exp(\eta_{1i})$ $\alpha_i = \alpha\left(\frac{bMMSE_i}{21}\right)\left(\frac{30-bMMSE_i}{9}\right)^{\theta 2} + \eta_{2i}$ $\eta_{1i} \sim N(0, \omega_1^2); \eta_{2i} \sim N(0, \omega_2^2); \varepsilon \sim N(0, \sigma^2)$	63,106.0	3	63,112
Linear progression model #4 with shape parameters θ1 and θ2 (Ito 2010)	$R_i(t) = R_{0i} + \alpha_i \cdot t + \varepsilon$ $R_{0i} = R_0 \cdot \exp(\eta_{1i})$ $\alpha_i = \alpha\left(\frac{bMMSE_i}{21}\right)^{\theta 1}\left(\frac{30-bMMSE_i}{9}\right)^{\theta 2} + \eta_{2i}$ $\eta_{1i} \sim N(0, \omega_1^2); \eta_{2i} \sim N(0, \omega_2^2); \varepsilon \sim N(0, \sigma^2)$	63,100.6	4	63,109
Linear progression model #5 with αi dependent on bMMSE$_i$ via a power relationship (Ito 2010)	$R_i(t) = R_{0i} + \alpha_i \cdot t + \varepsilon$ $R_{0i} = R_0 \cdot \exp(\eta_{1i})$ $\alpha_i = \alpha\left(\frac{bMMSE_i}{21}\right)^{\theta} + \eta_{2i}$ $\eta_{1i} \sim N(0, \omega_1^2); \eta_{2i} \sim N(0, \omega_2^2); \varepsilon \sim N(0, \sigma^2)$	63,159.9	3	63,166
Exponential progression model (Faltaos 2011; Yang 2011)	$R_i(t) = R_{0i} \cdot \exp(\alpha_i \cdot t) + \varepsilon$ $R_{0i} = R_0 \cdot \exp(\eta_{1i})$ $\alpha_i = \alpha + \eta_{2i}$ $\eta_{1i} \sim N(0, \omega_1^2); \eta_{2i} \sim N(0, \omega_2^2); \varepsilon \sim N(0, \sigma^2)$	62,998.6	2	63,003
2-Parameter logistic model[†] (Samtani 2012)	$R_i(t) = \frac{70 \cdot R_{0i}}{(70-R_{0i})e^{-\alpha i t} + R_{0i}} + \varepsilon$ $R_{0i} = R_0 \cdot \exp(\eta_{1i})$ $\alpha_i = \alpha + \eta_{2i}$ $\eta_{1i} \sim N(0, \omega_1^2); \eta_{2i} \sim N(0, \omega_2^2); \varepsilon \sim N(0, \sigma^2)$	63,318.1	2	63,322
Richard's function[‡] (Samtani 2012; Tsoularis 2002)	$R_i(t) = \frac{70 \cdot R_{0i}}{[(70^{\beta}-R_{0i}^{\beta})e^{-\alpha i \beta t} + R_{0i}^{\beta}]^{\frac{1}{\beta}}} + \varepsilon$ $R_{0i} = R_0 \cdot \exp(\eta_{1i})$ $\alpha_i = \alpha + \eta_{2i}$ $\eta_{1i} \sim N(0, \omega_1^2); \eta_{2i} \sim N(0, \omega_2^2); \varepsilon \sim N(0, \sigma^2)$	62,877.0	3	62,883

Abbreviation: AIC, Akaike information criterion; bMMSEi, baseline Mini Mental State Examination in i[th]-patient.
*Akaike information criterion is equal to the objective function value plus twice the number of θs in a given model.
[†]This model is the explicit solution of the differential equation: dRi/dt = αi·Ri·(1−[Ri/70]); Ri(0) = R0i.
[‡]This is Richard's function and is the explicit solution of the differential equation: dRi/dt = αi·Ri·(1−[Ri/70]β); Ri(0) = R0i.

data mechanisms, and to confirm the assumption proposed for MAR.

A grouped-time survival model [22,23] was used to evaluate missing data from these studies:

where, α1…α6 are intercept parameters that characterize baseline hazards at different periods (e.g. 0–13 weeks); PD_{ij-1} is the PD score for the i-th patient at (j−1)th time period (relationship between the probability of dropout

$$\log(-\log(1-P[Dropout=1])) = [\alpha_1 D_{0-13} + \alpha_2 D_{13-26} + \alpha_3 D_{26-39} + \alpha_4 D_{39-52} + \alpha_5 D_{52-65} + \alpha_6 D_{65-78}] + \beta_1 PD_{ij-1} + \beta_2 (bAge_i - 74) \quad (2)$$

Table 2
Summary of residual error models

Model description	Residual error models	Objective function value	Number of θs	AIC* value
Normal distribution (Burnham 2002)	$l_i=-\frac{1}{2}\log(2\pi\sigma^2)-\frac{(y_i-\mu_i)^2}{2\sigma^2}$	−32,496	3	−32,490
Log-normal distribution (Burnham 2002)	$l_i=\log\left(\frac{1}{y_i}\right)-\frac{1}{2}\log(2\pi\sigma^2)-\frac{(\log(y_i)-\mu_i)^2}{2\sigma^2}$	−30,584	3	−30,578
Logit-normal distribution (Frederic 2008)	$l_i=\log\left(\frac{1}{y_i(1-y_i)}\right)-\frac{1}{2}\log(2\pi\sigma^2)-\frac{(\mathrm{logit}(y_i)-\mu_i)^2}{2\sigma^2}$	−32,344	3	−32,338
Beta distribution (Smithson 2006)	$l_i=\log\Gamma(\tau)-\log\Gamma(\mu_i\tau)-\log\Gamma((1-\mu_i)\tau)+(\mu_i\tau-1)\log(y_i)+((1-\mu_i)\tau-1)\log(1-y_i)$	−32,948	3	−32,942

Abbreviation: AIC, Akaike information criterion.
*Akaike information criterion is equal to the objective function value plus twice the number of θs in a given model.

and PD score before dropout); D (e.g. $D_{0–13}$) is a dummy variable coded as 1 if observation represents the corresponding interval (e.g. 0–13 weeks), otherwise coded as 0.

2.6. Model qualification

After finalization of the disease progression, placebo course, covariates, and dropout submodels, model qualification was performed in which goodness-of-fit plots were generated; precision/plausibility of the model parameters was assessed; and the observed data were visually compared using VPCs with simulated data at respective time points (weeks 0, 13, 26, 39, 52, 65, and 78). In addition, Pearson residuals (standardized ordinary residuals) were used for beta regression. The level to which the median prediction and extremes of 90% prediction interval replicated the median, 5th, and 95th percentiles of the observed data was evaluated using percentile VPC with confidence intervals [24].

2.7. Placebo model

The structural form of the placebo function was selected based on prior research [15], and inverse Bateman function and exponential functions were explored to describe the course of the placebo group. Within-placebo arms of both studies, an initial period of weeks or months when little or no change in ADAS-cog scores was evident, suggesting that a time-dependent placebo effect was present and was modeled accordingly.

2.8. Final PK/PD model

The impact of bapineuzumab exposure on disease progression was visualized by graphical exploratory analysis. This exploratory analysis addressed two critical and relevant questions about (1) treatment and dose effect, and (2) influence of *APOE* ε4 carrier status or baseline disease status on treatment effect. Depending on baseline MMSE score (mild AD ≥21 definition from National Institute for Health and Clinical Excellence 2011), the patient population was dichotomized into two groups to visualize the influence of disease status on the drug effect.

The exposure-response modeling was performed to facilitate improved understanding of the drug effect, and to assess the magnitude of the effect. A sequential PK/PD modeling approach was used, and individual PK parameters were fixed to their individual Bayesian estimates. As bapineuzumab is a disease-modifying treatment, the drug effect was tested on a progression rate parameter to investigate its disease-modifying effects.

3. Results

The final data set contained ADAS-cog/11 measurements collected from 2451 patients with mild-to-moderate AD, who were randomized to bapineuzumab (n = 1480) or placebo (n = 971) over the 78-week duration of the studies. Detailed baseline patient characteristics of the two studies are published [12].

An overview of the model building process is provided as a flowchart in Fig. 1. Sections 3.1, 3.2, 3.3, 3.4, and 3.5 describe the results of the following submodels of the overall disease progression model: structural model, residual error model, covariate model, placebo model, and drug treatment model, respectively.

3.1. Selection of regular structural models versus beta regression models

Richard's function with the regular parameterization (Richard's function with additive residual error) was most appropriate to describe AD progression over time as assessed by AIC. The reason it performed better than the exponential and progression models was because the other models allowed an increase in ADAS-cog/11 scores without any restriction (which is not mechanistic). Among the three beta regression models tested, Richard's function also had the lowest AIC. Thus, the same structural model was chosen for both regular parameterization (normally distributed errors) and beta regression.

3.2. Optimal residual error model and boundary data handling

The residual error parameterization with the lowest AIC value was the beta distribution. Richard's function with beta residuals was chosen as the base model for covariate model building. As recommended in published reports [19,20], all data were rescaled by a δ value of 0.01, and these rescaled data were used in further testing of the model.

3.3. Covariate effects on disease progression parameters

3.3.1. Base reference model: Prior knowledge about covariate effects

An exploratory graphical analysis was conducted before covariate model building to assess the influence of five selected covariates on disease progression. All covariates (age, YSO, sex, *APOE* ε4 carrier status, and concomitant AD medications) were found to have a low degree of correlation. This graphical analysis confirmed prior knowledge about covariate effects on disease progression (Fig. 2). Generally, cognitive performance of *APOE* ε4 carriers, women, younger patients, and patients with longer AD duration was found to be poor (i.e., any of these covariates could increase ADAS-cog/11 score in a univariate manner). Furthermore, the impact of age, sex, and *APOE* ε4 trichotomous carrier status (ε4 noncarrier, ε4 heterozygous, and ε4 homozygous) on disease progression rate and influence of YSO on baseline score were incorporated into the model as follows (equation 1) based on prior knowledge and graphical analysis:

$$R_{0i} = \theta_{Ro} \cdot e^{YSO \cdot \theta Ro\_YSO} \cdot e^{\eta 1i} \quad (3)$$

$$\alpha_i = \theta_{\alpha} \cdot \left(\frac{AGE_i}{74}\right)^{-\theta\alpha\_AGE} Sex\_\alpha_i \cdot ApoE4\_\alpha_i + \eta_{2i} \quad (4)$$

where, θs represent various fixed-effect parameters; Sex_αi is 1 for women and θα_sex for men;

ApoE4_αi is 1 for patients with one *APOE* ε4 allele; θα_ApoE4_0 for patients with zero *APOE* ε4 alleles, and θα_ApoE4_2 for patients with two *APOE* ε4 alleles.

This updated model was referred to as the base reference model, which showed significant improvement over the base model, as measured by the OFV (ΔOFV = 78.5; *P* value <.0001; degrees of freedom [df] = 5). As expected, baseline disease status had a significant impact on disease progression (Fig. 2), whereas baseline ADAS-cog/11 score and progression rate differed according to AD concomitant medications use, and therefore, these were subsequently assessed in detail.

3.3.2. Newly identified covariates in the current analysis

For the covariate search, the next step was a screening procedure (GAM + R software). The η shrinkages on the baseline (4%) and progression rate parameters (22%) suggested suitability of individual η values for covariate screening.

All influential covariates from the screening procedure were added to the base reference model by means of appropriate functional forms to generate the full covariate model:

$$R_{0i} = \theta_{Ro} \cdot e^{YSO \cdot \theta Ro\_YSO} \cdot \left(\frac{AGE_i}{74}\right)^{\theta Ro\_AGE} \cdot Sex\_R_{0i} \cdot ApoE4\_R_{0i} \cdot Comed\_R_{0i} \cdot e^{\eta 1i} \quad (5)$$

$$\alpha_i = \theta_{\alpha} \cdot e^{-YSO \cdot \theta\alpha\_YSO} \left(\frac{AGE_i}{74}\right)^{-\theta\alpha\_AGE} \cdot Sex\_\alpha_i \cdot ApoE4\_\alpha_i \cdot Comed\_\alpha_i + \eta_{2i} \quad (6)$$

where, Sex, *APOE* ε4, and YSO were incorporated in a similar manner as the base reference model; Comed_R_{0i} and Comed_α_i:1 for patients taking acetylcholinesterase inhibitors alone, $\theta_{Ro\_Comed\_0}$ and $\theta_{\alpha\_Comed\_0}$: 0 for patients taking no AD concomitant medications, $\theta_{Ro\_Comed\_1}$ and $\theta_{\alpha\_Comed\_1}$: patients taking memantine alone, and $\theta_{Ro\ Comed\ 2}$ and $\theta_{\alpha\_Comed\_2}$: patients taking acetylcholinesterase inhibitors and memantine

The full covariate model was significantly improved over the base reference model with OFV change of 270 points (*P* value <.0001, df = 11). The final covariate model after backward elimination is presented in Table 3.

3.4. Placebo model

An exponential placebo model was found to be suitable for describing the transient improvement (or lack of deterioration) in cognitive symptoms, as characterized by an initially flat shape of ADAS-cog/11 trajectory mainly driven by study 301 which had milder patients and more amyloid-negative patients (unlikely to have AD), and it was further observed that patients with higher MMSE scores (i.e. milder cognitive impairment) had a greater transient improvement. The half-life for the development of the placebo course was 10 weeks. The relationship between baseline disease status and magnitude of placebo course was found to be highly significant (Fig. 3), warranting its addition into the model.

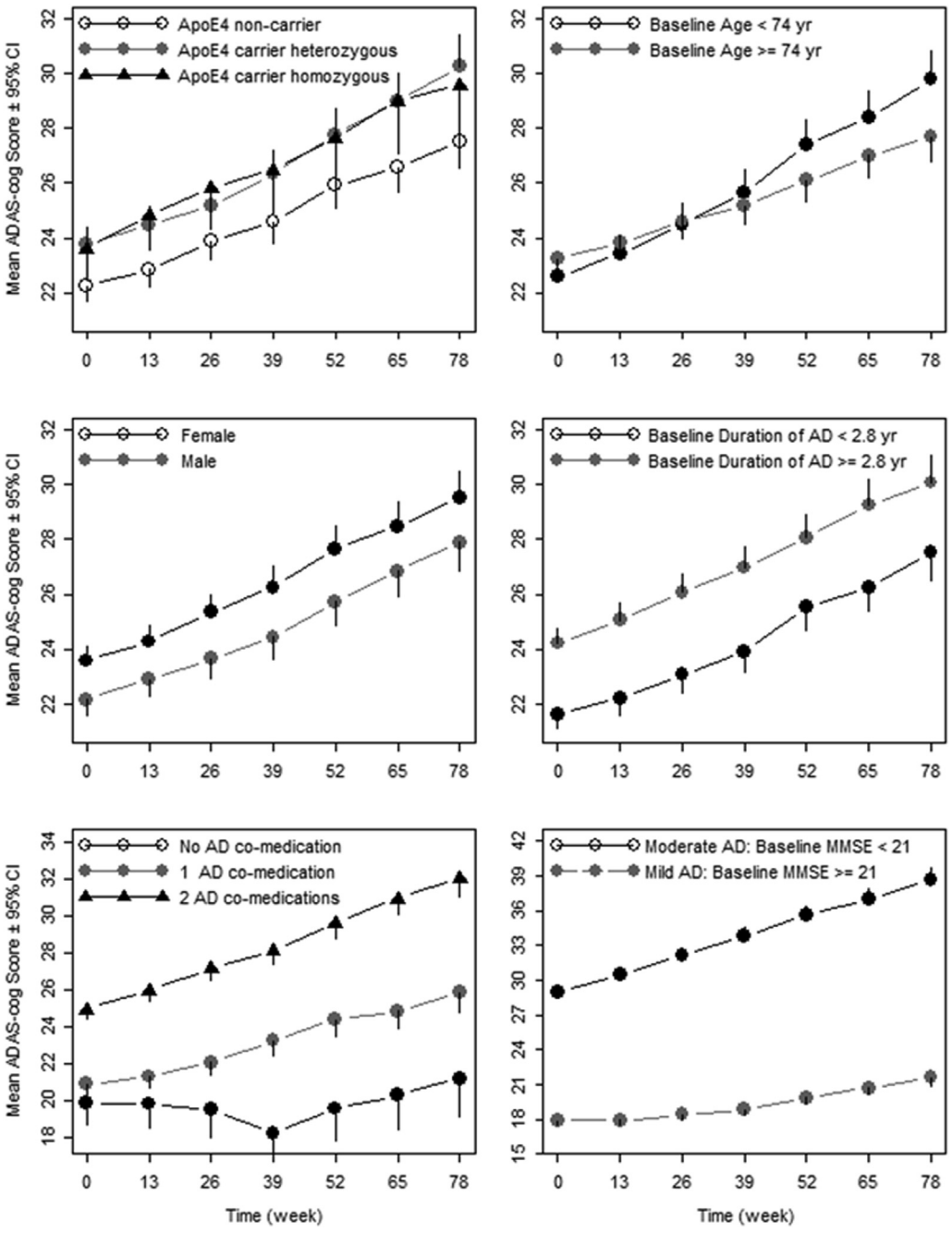

Fig. 2. Results of the exploratory placebo covariate analysis. Two Alzheimer's disease concomitant medications: acetylcholinesterase inhibitors and memantine; one Alzheimer's disease concomitant medication: acetylcholinesterase inhibitors alone or memantine alone. Responses are scaled to a 0–1 range for data analysis but for plotting the graphical results are back transformed to present the model performance on the original scale. Abbreviations: ADAS-cog/11, Alzheimer's disease assessment scale-cognitive 11-item; AD, Alzheimer's disease; *APOE* ε4, apolipoprotein E, ε4 allele; CI, confidence interval; MMSE, mini-mental state examination.

3.5. Final model

The placebo submodel with structural, covariate, and residual error components of the model was used as a reference model to test the effect of bapineuzumab treatment.

Bapineuzumab treatment effect was not significant as indicated by reduction in the OFV by 0.03 points (P value = .872, df = 1). Furthermore, formal testing of bapineuzumab exposure suggested that it was not a significant factor affecting disease progression (steady-state area under curve: ΔOFV = 0.02, P value = .888; steady-state C_{trough}: ΔOFV = 0.22, P value = .641). This lack of exposure-response relationship was in agreement with the exploratory exposure-response plots, showing temporal profiles separately for low- and high-exposure groups.

Table 3
Final ADAS-cog/11 model parameter estimates

Parameter*	Estimate	%CV†
θRo	19.2	1.9
θRo_YSO	0.017	20
θRo_SEX	0.938	1.6
θRo_ApoE4_0	0.952	1.6
θRo_Comed	1.190	1.6
θα	0.219	5.8
θα_YSO	0.0506	22
θα_AGE	1.08	15
θα_SEX	1.05	4.4
θα_ApoE4_0	0.96	4.8
θα_ApoE4_2	1.00	6.5
θα_Comed	1.11	5.0
θplbmax	0.696	13
θMMSE	0.582	10
θkplb	3.59	13
β‡	6.03	17
SD of η1§	0.377	3.4
SD of η2§	0.171	7.2
Residual error parameter τ	76.0	2.1

Abbreviations: ADAS-cog/11, Alzheimer's disease assessment scale-cognitive 11-item; CV, coefficient of variation; SD, standard deviation.

NOTE. All covariate effects reported in this table were significant at the 0.005 level. Between the base model and final covariate model, the between-patient variability SD estimates improved from 0.445 and 0.202 to 0.377 and 0.171, respectively.

*These equations describe the relationships between covariates and the parameters in the final model:

$R_{0i} = 19.2 \cdot e^{YSO \cdot 0.017} \cdot Sex\_R_{0i} \cdot ApoE4\_R_{0i} \cdot Comed\_R_{0i} \cdot e^{\eta 1i}$

$\alpha_i = 0.219 \cdot e^{-YSO \cdot 0.0506} \left(\frac{AGE_i}{74}\right)^{-1.08} \cdot Sex\_\alpha_i \cdot ApoE4\_\alpha_i \cdot Comed\_\alpha_i + \eta_{2i}$

$\text{Placebo Response} = \left[\frac{(-0.696) - 0.582 \cdot (\text{Baseline MMSE}_i - 21)}{70}\right] \cdot (1 - e^{-3.59 \cdot t})$, where,

R0i is the individual baseline score, αi is the individual progression rate parameter; Sex_R0i is 1 for women *and* θRo_SEX for men; ApoE4_R0i is 1 for patients with 1 or 2 E4 alleles and θRo_ApoE4_0 for patients with 0 E4 allele; Comed_R0i is 1 for patients taking 0 or 1 Alzheimer's disease concomitant medications and θRo_Comed for patients taking acetylcholinesterase inhibitors and memantine; Sex_αi is 1 for women and θα_SEX for men; ApoE4_αi is 1 for patients with 1 APOE * E4 allele, θα_ApoE4_0 for patients with 0 *APOE* ε4 alleles, and θα_ApoE4_2 for patients with 2 *APOE* ε4 alleles; Comed_αi is 1 for patients taking acetylcholinesterase inhibitor alone or memantine alone, 0 for patient takings no Alzheimer's disease concomitant medications, and θα_Comed for patients taking acetylcholinesterase inhibitors and memantine.

†%CV represents precision of parameter estimate.

‡Final estimated inflection point is 51 based on the formula (70β/[1 + β]) 1/β.

§Off-diagonal element of covariance matrix: covariance η1,η2 = 0.00988 (%CV = 28.3%); correlation between ρ and α, r = (covariance η1,η2/[SD η1 · SD η2]) = 0.153 and r^2 = 0.024.

There was no evidence of treatment effect in either *APOE* ε4 subgroups or in mild versus moderate AD patients. Thus, the reference model without bapineuzumab effect was considered as the final ADAS-cog/11 disease progression model (Table 3).

The VPCs (that accounted for dropout) suggested that the final model without the influence of bapineuzumab describes longitudinal progression of ADAS-cog/11 scores reasonably well in both the bapineuzumab and placebo arms, indicating no treatment effect in the overall ADAS-cog/11 disease progression data set. The stratification of patients with mild AD suggested that the model was able to describe the temporal, initially flat profile for the placebo course, which is much more prominent in mild AD patients. This supports placebo subcomponent of the final disease progression model for ADAS-cog/11 score.

A formal analysis confirmed that the likelihood of missing data was dependent on the ADAS-cog/11 score before the event and the patient's baseline age (Table 4). The dependence on both these variables was highly significant ($P < .0001$). Hazard ratios indicated that there was a 4% increase in the hazard of dropping out (i.e., data being missing) with either 1 point increase in ADAS-cog/11 score or a 1-year increase in baseline age. This finding confirmed that "missing completely at random" was not the missing data mechanism and that MAR may be a more reasonable assumption, which was consistent with the assumption for the primary statistical analysis (MMRM).

4. Discussion

In this analysis, after thoroughly investigating various structural models available in the literature [5,7,14–16,18], a semimechanistic model was developed to describe AD progression (measured by ADAS-cog/11 scores) in patients treated with bapineuzumab and placebo. The model is considered semimechanistic because it accommodates the nonlinear nature of AD progression and also accounts for floor and ceiling effects.

Eight different linear and nonlinear structural models (Table 1) were compared in the current analysis and all these models have been used in the literature to describe ADAS-cog/11 progression. There is no consensus in the literature about which approach is more suitable than the other. It

Table 4
Parameter estimates from the dropout model

Parameter	Estimate	CV%
Baseline hazard (α parameters)		
Period 1 in weeks (0,13)	−4.320	3.15
Period 2 in weeks (13,26)	−4.031	3.18
Period 3 in weeks (26,39)	−3.904	3.25
Period 4 in weeks (39,52)	−4.042	3.36
Period 5 in weeks (52,65)	−3.865	3.49
Period 6 in weeks (65,78)	−4.319	3.57
Coefficients (β parameters)		
ADAS-cog/11 score before dropout	0.039*,***	
Baseline age	0.038*,***	

Abbreviations: CV, coefficient of variation; ADAS-cog/11, Alzheimer's disease assessment scale-cognitive 11-item.

NOTE. ***$P < .0001$; (lower boundary, upper boundary) indicates that the range includes the lower boundary but not the upper boundary.

*Hazard ratios can be obtained by exponentiating these parameter estimates, i.e., indicating there is approximately a 4% increase in the hazard of dropping out because of data being missing with either 1 point increase in ADAS-cog/11 score or a 1 year increase in age.

may appear that a linear-mixed model for repeated measures may suffice to model the general profile of the response, and exceptions (e.g., mild AD plots) could be modeled using the change point models from the statistical literature. However, the nonlinear kinetic models offer potential advantage of modeling both the general profile and the exceptions together with a single equation such as the Richard's function. Furthermore, the transformed residual error models describe the floor and ceiling effects and may lead to more effective use of data. A key strength of the current analysis is that these various approaches of modeling disease progression data have been formally compared, and to the best of our knowledge, this is the first study that does such a comparison for ADAS-cog/11 data. The analysis reveals that the Richard's function is the most appropriate model based on model diagnostic criteria and semimechanistic considerations (described in Section 3.1) for the current set of data which represents a large database of 2451 patients.

Several approaches, such as linear, exponential, and logistic structural models, were formally compared to model the change in ADAS-cog scores seen in bapineuzumab- or placebo-treated patients with mild-to-moderate AD. Of the models tested, linear and exponential models are known to predict scores outside the range (0–70) of ADAS-cog/11 scale. To circumvent this limitation and to allow the model to fulfill general expectation that disease progression is nonlinear in AD, a general logistic model was chosen for further development. However, the general logistic model had a disadvantage that it required the inflection point (ADAS-cog/11 score with fastest progression rate) to be at the midpoint of the scale. Inclusion of a shape parameter (β) in the final disease progression model remedied this problem and enhanced its fit to the data, and, therefore, the inflection point was estimated to be at ADAS-cog/11 score of 51 from the current analysis.

ADAS-cog/11 scale is bounded between 0 and 70, and scores theoretically plateau as deterioration progresses and scores approach 70 because of floor effects, which makes it difficult to measure the change in disease status in patients with severe AD. Thus, use of other clinical end points such as the severe impairment battery is recommended for severe AD [4]. In the current analysis, we mathematically described plateauing effect using Richard's function. Some of the salient features of the final disease progression model are as follows: First, the random effect on the baseline scores was assumed to follow a log-normal distribution, which was advantageous over the normal distribution in that it did not predict negative baseline scores at the individual level. Second, the random effect on the progression rate parameters was assumed to follow a normal distribution. This allowed greater flexibility to accommodate the wide range of progression rates at the individual level (disease status improved, deteriorated, or remain unchanged), as observed in studies 301 and 302.

In the current analysis, different types of residual error structures (normal, log-normal, logit-normal, and beta distribution) were tested, and beta distribution was found to capture the behavior of the residual error most appropriately. Two main advantages of residual error structure include model predictions, even after accounting for residual error, stayed within ADAS-Cog/11 scale boundaries. Second, beta residuals accounted for interdependence between the mean and variance of the data structure. The variance was generally lower as scores approached the edges of the scale, whereas variance was greater around middle portion of the scale, and beta residuals could accommodate this complexity. It is noteworthy that implementation of beta residuals in NONMEM is not common because it can be technically challenging (the beta distribution is not built into the software).

The rate of disease progression varies among AD patients; however, there is limited awareness of prognostic factors for disease progression in mild-to-moderate AD patients. Our model accounted for many of the previously known disease progression covariates measured by ADAS-cog/11 scores. The current data set of studies 301 and 302 confirmed the impact of AD duration on baseline score and the influence of age and *APOE* ε4 carrier status on disease progression rate. These findings corroborate the high quality of that data that were obtained in these two studies. The high quality of the data is further confirmed by the model prediction that the progression rate in a typical patient (i.e., with median values of the relevant covariates) was 5 ADAS-cog/11 points per year for a 74-year-old woman with 1 *APOE* ε4 allele, taking one AD concomitant medication, with a baseline ADAS-cog/11 score of 23, and recently diagnosed with AD. These estimates are consistent with a progression rate of 5.5 ADAS-cog/11 points per year in the placebo group which is generally well accepted in the published AD literature [4,15]. In addition, the richness of data in studies 301 and 302 offered several opportunities to possibly investigate an expanded list of potential covariates of interest available in the data set. The influence of sex on progression rate has been reported [4], in which they observed a small but not significant, slow progression rate (10.7%) in men with AD. In our analysis, the influence of sex on progression rate was also tested and a small, 5% faster progression rate parameter was observed in men versus women. A recent, large meta-analysis (with >3000 patients) has also investigated the impact of sex on ADAS-cog/11 progression rate [2], which concluded that disease progresses at a faster rate in men than women (although it was not significant at the 0.05 level). Collectively, in the light of available literature and current analysis, the impact of sex on AD progression rate appears to be rather minimal.

Literature linking association of *APOE* ε4 allele with cognitive deterioration varies. The current analysis also allowed assessment of whether homozygous *APOE* ε4 carriers (11% of the overall population) were different from heterozygous *APOE* ε4 carriers (34% of the overall population) in terms of disease progression. It revealed that *APOE* ε4 noncarriers had both a lower baseline ADAS-cog/11 score and a slower progression rate than *APOE* ε4 carriers, and

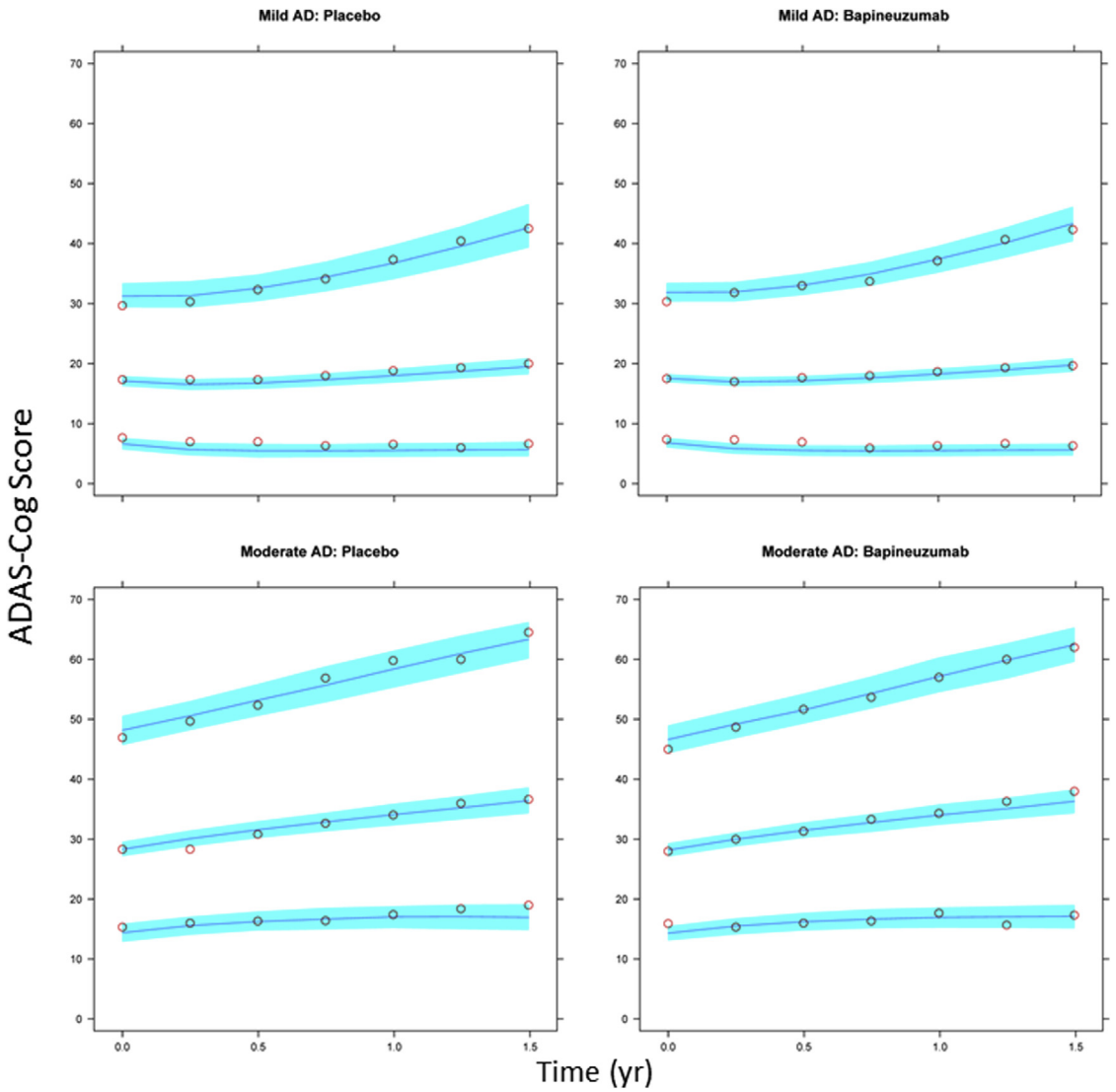

Fig. 3. Stratified visual predictive checks: bapineuzumab versus placebo. The upper, middle, and lower profiles indicated by the open circles represent 95th, 50th, and 5th percentiles of the observed data, respectively. The upper, middle, and lower curves indicated by the lines are the median model–based predictions for 95th, 50th, and 5th percentiles, respectively, and these predictions account for missing data. The shaded areas are 90% confidence intervals of the corresponding percentiles of the simulations based on the model. To allow stratification by baseline disease status (mild AD vs. moderate AD), baseline ADAS-cog/11 scores were resampled from the observed scores at time 0 in the respective populations from the PK/PD database. The number of observations at 0, 13, 26, 39, 52, 65, and 78 wk were 2451, 2331, 2215, 2093, 1989, 1870, and 1808 and thus 74% of patients (1808/2451) completed the study. Seventy-four years (age) and 2.8 y (duration of AD) used as cutoffs in the figures represents the median. Abbreviations: ADAS-cog/11, Alzheimer's disease assessment scale-cognitive 11-item; AD, Alzheimer's disease; CI, confidence interval; PK/PD, pharmacokinetic/pharmacodynamic.

there was no difference in the modeled baseline score or progression rate between those subgroups (Table 3). This trend was also confirmed by the exploratory graph presented in Fig. 2.

The impact of AD concomitant medication use illustrated some differences among the patients recruited in the two studies [25]. Patients taking memantine and acetylcholinesterase inhibitors (53% of overall population) had both a higher baseline ADAS-cog/11 score and a faster progression rate parameter that was 11% higher than that expected from the higher baseline score alone. Thus, confirming that patients requiring both AD concomitant medications represented a subgroup with poorer cognitive function and, therefore, progress faster, whereas patients not taking any AD concomitant medications (10% of the overall population, n = 232) had a progression rate that was not significantly different from 0 (P value = .154). Importantly, there were more *APOE* ε4 noncarriers (146/232) who were not taking any AD concomitant medications. Assessment of covariates affecting baseline severity revealed that men had a 6% lower baseline ADAS-cog/11 score than women; patients who took two AD concomitant medications had a 19% higher (worse) baseline score; *APOE* ε4 noncarriers had a 5% lower baseline score; and patients who had AD for a longer duration had a higher baseline score. Furthermore, shorter AD duration, younger

age, *APOE* ε4 carrier, and use of two AD concomitant medications were associated with faster disease progression rates.

Estimates from the current model suggest that progression rates change with baseline severity, decrease with increasing age and years since disease onset, *APOE* ε4 carriers progress more rapidly than noncarriers, and males progress at a faster rate than females. Most of these relationships are directionally consistent with previously reported associations. In contrast to the present study, other authors have observed that AD progresses at a faster rate in women than men [26,27]. One of the limitations of the present study is that the years of education was not included in the covariate submodel. The absence of this variable might have affected the result because men have higher education than women. However, a recent analysis [5] has shown that it is difficult to detect the influence of education on cognitive performance in clinical trials because clinical trial participants have higher levels of education i.e., the models are not able to describe this effect, likely because of the narrow distribution of years of education in the trial participants. Although few authors reported conflicting results for *APOE* ε4 genotype effect on the rate of AD progression [28,29], our results indicate that *APOE* ε4 carriers were found to progress more rapidly than noncarriers, which is consistent with the recent publications using larger studies [2,4,25]. Furthermore, differences in AD clinical trial outcomes based on age of the participants have been recently reported by Schneider et al. [30], younger age also found to be associated with faster disease progression [2,4,25]. The current analysis confirms that older groups of patients show slower rates of decline on the ADAS-cog than the younger groups. Finally, patients not taking any AD concomitant medications had a progression rate that was not significantly different from zero and this could partly be attributed to the amyloid-negative patients unlikely to have AD that were enrolled in these two bapineuzumab phase-3 studies. This is based on the Pittsburgh compound B-Positron emission tomography (PIB-PET) substudy of the 301/302 studies (n = 154) where a total of 6.5% of *APOE* ε4 carriers and 36.1% of *APOE* ε4 noncarriers were amyloid negative at baseline [11]. Recently, Samtani et al. [6] have shown that amyloid-negative patients do not exhibit decline in ADAS-cog/11 and the current model allows zero progression rate (and even improvement in cognition). This is possible through covariate effects such as comedication status and allowing the random effect on the slope parameter to be additive in nature allowing progression rate to positive, zero, and negative at the individual level.

The richness of the current data set also allowed delineation of the transient placebo course observed in both studies. Patients with milder AD and higher baseline MMSE scores had a transient lack of deterioration in cognitive symptoms at the beginning of the study (i.e., an initially flat shape was observed in the ADAS-cog/11 score trajectory). This phenomenon has also been recently seen in two other studies (large, 54-week clinical studies in AD involving 926 patients), wherein results of placebo-treated patients were published [31]. In the present study, the placebo course had a half-life of 10 weeks and the MMSE score was found to be a highly significant covariate for the amplitude of the placebo course.

The dropout process for this population exhibited the "healthy survivor effect", wherein as the ADAS-cog scores increased with cognitive decline, the probability of dropout increased. Thus, the completers had less disease severity and tended to be mild AD subjects compared with moderate AD subjects that tended to dropout. This phenomenon was captured in the model through the dropout submodel. Therefore, simulations for the VPC were performed with the combined disease progression plus dropout model. This joint prediction is particularly helpful with improving the predictive performance of the model at later times where scores are high and probability of dropout higher (for an illustration see Samtani et al. [17]).

The final step of this modeling exercise tested treatment and exposure-response effects of bapineuzumab on disease progression. The analysis suggested a "lack of treatment" effect in the overall population and various subpopulations. Although an exposure-response relationship could also not be elucidated, the model could still represent a suitable tool for clinical study simulation. The influential covariates on AD progression identified in this analysis could potentially be used for future study designs, identifying inclusion and exclusion criteria or stratification criteria, and for modeling outcomes.

One of the limitations of the present study is that the years of education was not included in the covariate submodel. The absence of this variable might have affected the result because men have higher education than women. However, a recent analysis [5] has shown that it is difficult to detect the influence of education on cognitive performance in clinical trials because clinical trial participants have higher levels of education i.e., the models are not able to describe this effect, likely because of the narrow distribution of years of education in the trial participants.

5. Conclusion

A beta regression model with Richard's function best described the disease progression as measured by ADAS-cog/11 scores in patients with mild-to-moderate AD. The influence of bapineuzumab exposure on disease progression was not significant and this is consistent with the results from the primary statistical analysis of the ADAS-cog/11 data and other efficacy data in studies 301 and 302. A placebo course was apparent in the current ADAS-cog/11 data set and the amplitude of the placebo course was dependent on baseline disease status, consistent with known learning effects in AD. Sex, AD concomitant medication use, Pittsburgh compound B-Positron emission tomography carrier status, and

YSO had significant effects on the baseline ADAS-cog/11 score, whereas AD concomitant medication use, age, YSO, and Pittsburgh compound B-Positron emission tomography carrier status had significant effects on the disease progression rate measured as ADAS-cog/11 scores.

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All authors contributed in the design of the analysis plan and interpretation of the data. M.N.S. and S.X.X. contributed equally in the analysis of the data. All authors met ICMJE criteria and all those who fulfilled those criteria are listed as authors. All authors had access to the study data, provided direction and comments on the article, made the final decision about where to publish these data, and approved the final draft and submission to this journal.

RESEARCH IN CONTEXT

1. Systematic review: ADAS-Cog/11 disease progression modeling was performed on pooled data from two phase-3 clinical studies of bapineuzumab in patients with mild-to-moderate AD.
2. Interpretation: The main aim of these current exploratory analyses was to model the longitudinal changes in ADAS-cog scores and to assess impact of exposure to bapineuzumab on disease progression. Although the treatment effect (bapineuzumab vs. placebo) was not statistically significant in both phase-3 studies, the pharmacokinetic concentration data collected in the studies provided a unique opportunity to evaluate the relationship between individual bapineuzumab exposure and disease progression of ADAS-cog scores. We observed that bapineuzumab exposure had no significant effect on ADAS-Cog progression; however, concomitant medication use, age, illness duration, and APOE*ε4 carrier status had significant effects on ADAS-Cog progression rate.
3. Future directions: Even though an exposure-response relationship was not found, the model could still represent a suitable tool for clinical trial simulation and could assist in the design of future clinical studies.

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